EU Risk Management Plan
for
Axitinib Accord 1 mg film-coated tablets
Axitinib Accord 3 mg film-coated tablets
Axitinib Accord 5 mg film-coated tablets
(Axitinib)

RMP version to be assessed as part of this application:

RMP Version number	2.1
Data lock point for this RMP	15-Nov-2024
Date of final sign off	06-Dec-2024

Rationale for submitting an updated RMP: This RMP has been updated in line with supplementary information further to Initial Assessment Report for Axitinib Accord (EMEA/H/C/006206/IB/0001) dated 15-Nov-2024.

Summary of significant changes in this RMP: Significant changes has been made in following sections of RMP: Addition of a targeted follow-up questionnaire regarding Torsade de pointes due to QT prolongation in Part III and Annex 4

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP: Not Applicable

Version	Procedure	Approval date
1.0	Centralised Procedure (EMEA/H/C/006206/0000)	25-Jul-2024

QPPV name: Dr. Arletta Werynska

QPPV signature: [redacted]

[redacted]

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Axitinib
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group:** Antineoplastic agents, protein kinase inhibitors **ATC code:** L01EK01
Marketing Authorisation Holder	Accord Healthcare S.L.U.
Medicinal products to which this RMP refers	01
Invented name(s) in the European Economic Area (EEA)	Axitinib Accord 1 mg film-coated tablets Axitinib Accord 3 mg film-coated tablets Axitinib Accord 5 mg film-coated tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/006206/0000)
Brief description of the product	Chemical class: Axitinib is an indazole substituted at position 3 by a 2-(pyridin-2-yl) vinyl group and at position 6 by a 2-(N-methylaminocarboxy) phenylsulfanyl group. It is a member of indazoles, a member of pyridines, an aryl sulfide and a member of benzamides.
	Summary of mode of action: Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the

	phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target in vivo and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.
	Important information about its composition: *Axitinib Accord 1 mg film-coated tablets* Each film-coated tablet contains 1 mg of axitinib. *Axitinib Accord 3 mg film-coated tablets* Each film-coated tablet contains 3 mg of axitinib. *Axitinib Accord 5 mg film-coated tablets* Each film-coated tablet contains 5 mg of axitinib. **Excipients with known effect:** *Axitinib Accord 1 mg film-coated tablet* Each film-coated tablet contains 54.2 mg of lactose. *Axitinib Accord 3 mg film-coated tablet* Each film-coated tablet contains 32.5 mg of lactose. *Axitinib Accord 5 mg film-coated tablet* Each film-coated tablet contains 54.2 mg of lactose.
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA	***Current:*** Axitinib Accord is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.
Dosage in the EEA	***Current:*** **Posology:**

	The recommended dose of axitinib is 5 mg twice daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. **Dose adjustments:** Dose increase or reduction is recommended based on individual safety and tolerability. Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions > Grade 2 (i.e. without severe adverse reactions according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) for two consecutive weeks may have their dose increased to 7 mg twice daily unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily. Dose adjustment is not required on the basis of patient age, race, gender, or body weight. Concomitant strong CYP3A4/5 inhibitors: Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations. Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

	Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy. If co administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered. Concomitant strong CYP3A4/5 inducers: Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations. Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended. Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. If co administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer. **Method of administration:** Axitinib is for oral use. They should be swallowed whole with a glass of water.

Pharmaceutical form(s) and strengths	***Current:*** Film-coated Tablets 1/3/5 mg
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

There is a European Public Assessment Report (EPAR) – summary of risk management plan available for the reference product Inlyta (axitinib) (Version 10.2, dated 16-May-2019) on the EMA website, published on 16-Aug-2024. There is no change proposed by the MAH in these safety concerns mentioned in Module SVIII, which is in line with summary of safety concerns for the reference product.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2 Presentation of the missing information

Not Applicable

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Arterial embolic and thrombotic events • Gastrointestinal perforation and fistula • Haemorrhage • Posterior Reversible Encephalopathy Syndrome • Venous Embolic and Thrombotic Event • Effects on the exocrine pancreas • Renal failure • Congestive heart failure/cardiomyopathy
Important potential risks	• Torsade de pointes due to QT prolongation • Reproductive and developmental toxicity • Carcinogenicity • Osteonecrosis of the jaw
Missing information	• Risks in pregnant and lactating women • Risks in paediatric subjects • Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN (Upper Limit of Normal) or calculated creatinine clearance <60 mL/min) • Risks in subjects with severe hepatic impairment (Child-Pugh Class C) • Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis • Risks in subjects with active peptic ulcer disease • Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for QT prolongation/Torsade de pointes:

To obtain structured follow up information for the important potential risk of Torsade de pointes due to QT prolongation, a Data Capture Aid (DCA) is being used by prescribers containing specific questions for QT related AEs. The DCA is provided in Annex 4

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the remaining safety concerns.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Management Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not Applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not Applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Axitinib Accord 1/3/5 mg film-coated tablets (Axitinib)

This is a summary of the risk management plan (RMP) for Axitinib Accord 1/3/5 mg film-coated tablets. The RMP details important risks of Axitinib Accord 1/3/5 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained for Axitinib Accord 1/3/5 mg film-coated tablets' risks and uncertainties (missing information).

Axitinib Accord 1/3/5 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Axitinib Accord 1/3/5 mg film-coated tablets should be used.

This summary of the RMP for Axitinib Accord 1/3/5 mg film-coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in the future updates of Axitinib Accord 1/3/5 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Axitinib Accord is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

It contains Axitinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Axitinib Accord 1/3/5 mg film-coated tablets' benefits can be found in Axitinib Accord 1/3/5 mg film-coated tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/axitinib-accord.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Axitinib Accord 1/3/5 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Axitinib Accord 1/3/5 mg film-coated tablets' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine *risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Axitinib Accord 1/3/5 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Axitinib Accord 1/3/5 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Axitinib Accord 1/3/5 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine):

Important identified risks	• Arterial embolic and thrombotic events • Gastrointestinal perforation and fistula • Haemorrhage • Posterior Reversible Encephalopathy Syndrome • Venous Embolic and Thrombotic Event

	• Effects on the exocrine pancreas • Renal failure • Congestive heart failure/cardiomyopathy
Important potential risks	• Torsade de pointes due to QT prolongation • Reproductive and developmental toxicity • Carcinogenicity • Osteonecrosis of the jaw
Missing information	• Risks in pregnant and lactating women • Risks in paediatric subjects • Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN (Upper Limit of Normal) or calculated creatinine clearance <60 mL/min) • Risks in subjects with severe hepatic impairment (Child-Pugh Class C) • Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis • Risks in subjects with active peptic ulcer disease • Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product Inlyta.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Axitinib Accord 1/3/5 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Axitinib Accord 1/3/5 mg film-coated tablets.

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed following targeted follow-up questionnaires for following risks;

- Torsade de pointes due to QT prolongation

QT Interval/Torsades de Pointes Data Capture Aid (DCA)

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report#: _____

Suspect Product: _____

Reported event term prompting special follow-up activities:_____

QT lnterval/Torsades de Pointes Follow-up Questions	
Please provide additional details on a separate page if needed, and reference the question number.	
1. Is the reported adverse event a: ☐ New event ☐ Recurrence *(please provide details on previous events)* ☐ Exacerbation of underlying condition *(please provide details)* *Details:*	
2. Please specify whether the patient has a history of any of the following: (please specify date of onset/ resolution)	
☐ Eating disorder	☐ Protein diets
☐ Laxative abuse	☐ Gastroplasty/ileojejunal bypass
☐ Celiac disease	☐ Acute nervous system injury
☐ CVA	☐ Hemorrhage
☐ Pheochromocytoma	☐ Hypothyroidism
☐ Impaired renal function	☐ Impaired liver function
☐ Bradycardia	☐ 2nd Degree AV block
☐ 3rd Degree AV block	☐ Recent therapeutic atrial fibrillation conversion
☐ MI	☐ Cardiomyopathy
☐ Mitral valve prolapse	☐ Recent heart surgery
☐ Recent catheterization or intracoronary dye	☐ Congenital long QT syndrome

☐ Concurrent hypothermia ☐ History of VTNEA

☐ Other (please specify)

Details:

3. **Please mark whether the patient was taking any of the following medications at the time of the adverse event or <u>within one month prior</u> to the onset of the adverse event:** (Please provide the specific dates of administration, dosage, and timing in relation to product)

Antiarrhythmic Drugs:

☐ Quinidine ☐ Disopyramide ☐ Procainamide ☐ Sotalol

☐ Amiodarone ☐ lbutilide ☐ Dofetilide ☐ Other *(Please specify)*

Antibiotics:

☐ Erythromycin ☐ Clarithromycin ☐ Fluconazole ☐ Ketoconazole

☐ Amantadine ☐ Pentamidine ☐ Other *(Please specify)*

Psychiatric Medications:

☐ Tricyclics ☐ Tetracyclics ☐ Other Antidepressants *(Please specify)*

☐ Thioridazine ☐ Haloperidol ☐ Sertindole

☐ Phenothiazines ☐ Other Antipsychotics *(Please specify)*

Antihistamines:

☐ Astemizole ☐ Other *(Please specify)*

Serotonin Receptor Antagonists:

☐ Ketanserin ☐ Other *(Please specify)*

Diuretics:

☐ Indapamide ☐ Triamterene ☐ Hydrochlorothiazide

☐ Other *(Please specify)*

Laxatives: *(Please specify)* _____

Inotropics:

☐ Amrinone ☐ Milrinone ☐ Other (Please specify)

Details:

4. **Were any of the following laboratory tests or diagnostic studies performed?** Please specify laboratory data with units, date of test, and reference ranges; and please provide printouts and photographs if available:

	Before Drug	**On Drug**	**After Drug Stopped**
Was an ECG or rhythm strip done?	☐ No ☐ Yes *(provide date)*	☐ No ☐ Yes *(provide date)*	☐ No ☐ Yes *(provide date)*
What was the actual QT interval?			
What was the QT c?			
Correction formula used?			
What was the corresponding heart rate?			
Was the ECG or rhythm strip automated and/or interpreted?	☐ Automated computer read out? ☐ Read by Physician? ☐ Read by Cardiologist?	☐ Automated computer read out? ☐ Read by Physician? ☐ Read by Cardiologist?	☐ Automated computer read out? ☐ Read by Physician? ☐ Read by Cardiologist?

Other Tests:

Laboratory Test	**Date Performed**	**Results with units if applicable**	**Reference Ranges if applicable**
☐ Potassium			
☐ Magnesium			
☐ Calcium			
☐ Thyroid studies			
☐ Other relevant tests *(please specify):*			